comparing the first nucleic acid sequence to a reference nucleic acid sequence or sequences, wherein the absence of the first nucleic acid sequence in the reference nucleic acid sequence or nucleic acid sequences indicates the first nucleic acid is a novel nucleic acid sequence.--

REMARKS

Upon entry of the present amendment, claims 1, 3-7, 9-20, and 27-32 will be pending in the application. Claims 2, 8 and 21-26 have been cancelled. Claims 21-26 have been cancelled as drawn to non-elected subject matter. Claims 1 and 20 have been amended. Support for the amendment to claim 1 appears in at least cancelled claims 2 and 8. Support for the amendment to claim 20 appears in at least claims 2 and 8 and at least original new claim 20 as filed.

Support for new claims 27-31 is found in at least Fig. 1 and on pages 4, lines 16-20, page 6, lines 20-22, pages 2-4 and pages 6-19. New claim 32 is supported in the specification in at least page 15, line 18 to page 16, line 6. No new matter has been added. An appendix showing claim amendments accompanies this response.

The claims are rejected for indefiniteness, anticipation, and obviousness.

Rejection under 35 USC § 112, second paragraph

Claim 20 was rejected as indefinite for omitting essential steps. The rejection is traversed to the extent that this claim is amended.

Claim 20 is drawn to a method of equalizing the representation of nucleic acids in a population of nucleic acid sequences. As amended, the claim requires "lowering the level of said

first nucleic acid sequence relative to the level of said second nucleic acid sequence in the subpopulation of nucleic acid sequences". The claim has been further amended to specify that the last recited step results in "equalizing the representation of nucleic acids in said population of nucleic acids". Therefore, as amended, the recited steps of claim 20 specify a method that results in equalization of the representation of nucleic acids in a sample of nucleic acids. Reconsideration and withdrawal of the rejection is requested.

Rejection under 35 USC § 102

Claims 1-3 and 7 were rejected under 35 U.S.C. § 102(b) as being anticipated by Adams Science, Vol. 252, pages 1651-1656, June 1991 ("Adams"). The rejection as applied to the amended claims is traversed.

Independent claim 1, from which depends claims 2, 3, and 7, has been amended to incorporate the subject matter of claim 8, which is not subject to the rejection. Accordingly, claim 1 as amended is not described by Adams. Reconsideration and withdrawal of the rejection is requested.

Rejection under 35 USC § 103

Claims 4-6 and 8-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Adams in view of Aggarwal et al., US Patent 5,824,509 ("Aggarwal"). The rejection is traversed to the extent that it is applied to the amended claims.

Claims 4-6 and 8-19 depend directly or indirectly from claim 1. As described above, claim 1 has been amended to require that wherein the partitioning step includes digesting the cDNA molecules with one or more restriction enzymes.

In order to establish a case of obviousness by combining references, there must be a suggestion or motivation for such a combination originating within the references themselves. The references must also be considered for their teachings considered as a whole. Further, the resulting combination must arrive at the claimed invention considered as a whole. Applicants' invention may not be used to generate the combination, for that is in fact the inventive act sought to be patented. Applicants demonstrate in the following argument that the references do not provide the requisite motivation for one of ordinary skill in the art to combine them.

The rejection represents selective hindsight reconstruction of the claimed invention. The Office Action has identified certain limitations in Adams. It selectively and inappropriately extracts those particular limitations from Aggarwal. In particular, the Office Action selects the cloning methods from Aggarwal without regard to the cloned material disclosed in Aggarwal, namely, the lymphotoxin gene. Aggarwal does not broadly disclose a cloning method, but only incidentally employs a particular method for cloning the lymphotoxin gene in order to transfect E. coli. Only selective hindsight provides the cloning method while dropping the cloned gene, as required for the combination in the Office Action to be sustained. Such selectivity is not permitted, for it ignores the broad scope of the teachings of Aggarwal considered as a whole.

Adams relates to identifying novel nucleic acid fragments that are not complete open reading frames, but rather are expressed sequence tags (ESTs). The method used by Adams includes automated partial DNA sequencing and can also include subtractive hybridization.

Aggarwal discloses methods related to developing biologically active lymphotoxin polypeptides (see Abstract). Lymphotoxin molecules are known glycoproteins (col. 1), so Applicants conclude that there is no need disclosed in Aggarwal to identify novel sequences. Aggarwal also introduces predetermined variations into lymphotoxin (col. 4, lines 10-11), again leading Applicants to conclude that there is no need disclosed in Aggarwal to identify novel sequences.

Applicants note that the Examiner cites Example 2 of Aggarwal for providing process steps that make lymphotoxin cDNA, ligate an adapter or linker, ligate an oligonucleotide into a cDNA and then transfect E. coli (Office Action, page 6). However, this citation does not relate to the problem of identifying novel nucleic acid sequences, since the lymphotoxins and linkers used in Aggarwal were known. The cited Example, or Aggarwal overall, in no way discusses a failing or need related to identifying novel nucleic acid fragments such as ESTs that would guide the artisan to consult Adams. Therefore, there is no motivation, teaching or suggestion in Aggarwal to combine its teachings with those of Adams

Additionally, Adams does not disclose any particular deficiency in their method or approach that would lead the artisan to learn how to prepare recombinant lymphotoxin as taught by Aggarwal. Adams furthermore does not disclose any deficiency related to use of restriction enzymes and cloning methods, especially cloning methods directed to cloning lymphotoxin proteins, since this reference already had available a cDNA library. Applicants conclude that Adams offers no motivation, teaching or suggestion to combine its teachings with those of Aggarwal.

Because the combination of Adams and Aggarwal fails to make obvious the claimed invention, reconsideration and withdrawal of the rejection is requested.

CONCLUSION

Applicants submit that the application is in condition for allowance, and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

A petition for extension of time is enclosed. The Commissioner is hereby authorized to charge payment of any additional filing fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 15966-539).

Respectfully submitted,

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APPENDIX SHOWING CLAIM AMENDMENTS

(1) (Amended) A method of screening a population of nucleic acids for a novel sequence, the method comprising:

providing a population of [nucleic acid sequences] cDNA molecules derived from a population of RNA molecules;

partitioning said population into one or more subpopulations of nucleic acids, wherein said partitioning comprises digesting the cDNA molecules with one or more restriction enzymes;

identifying a first nucleic acid sequence in the subpopulation of nucleic acid sequences; and

comparing the first nucleic acid sequence to a reference nucleic acid sequence or sequences, wherein the absence of the first nucleic acid sequence in the reference nucleic acid or nucleic acid sequences indicates the first nucleic acid is a novel nucleic acid sequence.

(20) (Amended) A method for equalizing the representation of nucleic acids in a population of nucleic acids, the method comprising in order the steps of:

providing a population of [nucleic acid sequences] cDNA molecules derived from a population of RNA molecules, wherein said population comprises a first nucleic acid and a second nucleic acid having a nucleic acid sequence distinct from the first nucleic acid, and wherein said first nucleic acid is present at a higher level in said population than said second population;

partitioning said population into one or more subpopulations of nucleic acids, wherein said partitioning comprises digesting the cDNA molecules with one or more restriction enzymes; and

[comparing] lowering the [levels] level of said first nucleic acid sequence relative to the [levels] level of said second nucleic acid sequence in the subpopulation of nucleic acid sequences, [wherein a lower level of the first nucleic acid sequence relative to the second nucleic acid sequence indicates the representation of said first and second nucleic acid sequences are normalized] thereby equalizing the representation of nucleic acids in said population of nucleic acids.